

REMARKS

The Examiner acknowledges receipt of Applicant's *Appeal Brief* dated 6-13-06, notes that Claims 1-8 and 31-36 have been pending. The Examiner further indicates that states that, upon reconsideration, the finality of the rejection of the last *Office Action* is withdrawn, the rejection set forth below has now been applied, and that Applicant's arguments with respect to claims 1-8 and 31-36 have been considered but are moot in view of the new ground of rejection.

Claim Rejections - 35 USC § 103

Claims 1-8 and 31-36 stand rejected under 35 U.S.C. 103(a) as being unpatentable over US 6,372,252 to Blume et al (Blume) in view of US 5,032,406 to Dansereau et al (Dansereau).

The Examiner states that Blume teaches immediate and sustained release formulations comprising guaifenesin, that Blume teaches loading guaifenesin and methocel into a high shear mixer, mixed at high speed, adding water and further mixing at additional time to complete granulation. The Examiner further states that the composition is next dried in fluid dryer and then passed through a mill fitted a suitable size screen (col. 7, lines 63 through col. 8, lines 23) and concludes that the resulting material of Blume reads on agglomerated mixture because the processing of the material involves the same steps as described in the instant application. The Examiner acknowledges that Blume fails to teach granulation of guaifenesin with polyvinylpyrrolidone.

The Examiner states that Dansereau teaches a tablet composition that provides dual action, for immediate and sustained release, comprising an outer tablet and an inner tablet respectively, wherein the active ingredient of both inner and outer tablets comprises guaifenesin. The Examiner further states that the

inner tablet particularly comprises guaifenesin and polyvinylpyrrolidone (example I) and points out that Dansereau teaches making the inner tablet by wet granulating of guaifenesin and polyvinylpyrrolidone, drying the granulation, and screening the granulation through a 12 mesh screen (as described at col. 6 of Dansereau). The Examiner urges that the resulting inner tablet composition of Dansereau reads on the claimed agglomerate mixture because the process involves the same steps as described in the instant specification (page 3, lines 15-20).

The Examiner concludes that It would have been obvious for one of an ordinary skill in the art at the time of the instant invention to employ polyvinylpyrrolidone or methocel for the processing and preparation of compressible guaifenesin tablets because Dansereau recognizes methylcellulose and polyvinylpyrrolidone as both binders as well as disintegrants and the prior art references both the excipients as suitable for preparing a sustained release compressible tablet preparation comprising guaifenesin.

Applicant acknowledges that Blume discloses guaifenesin compositions, but submits that Blume does not satisfy the limitations of Applicant's claim 1 because, as acknowledged by the Examiner, Blume fails to disclose the agglomerate of guaifenesin and polyvinylpyrrolidone required by Applicant's claim 1 and because, as acknowledged by the Examiner, Blume fails to disclose the particle size distribution required by Applicant's claim 1. Applicant further acknowledges that the Blume describes making guaifenesin/methocel granulation by wet granulating a mixture of guaifenesin and methocel, drying the granulation and then milling the dry granulation, but submits that the process disclosed by Blume differs significantly from that described in the present application and used to make the compositions of Applicant's Examples 1 -10. The process described by Blume differs from the process described in the present application with respect to, at least: (a) the wet milling of Applicant's agglomerate (see p. 9, lines

1 -11 of the present specification), (b) the selection of process conditions required to satisfy Applicant's claimed particle size distribution (see p. 10, line 12 to p. 11, line 8 of the present specification), and (c) the separation, dry milling, and subsequent reintroduction to Applicant's claimed composition of particles that initially exceeded a particle size classification limit (see p. 3, lines 23- 25 and p. 10, lines 11 - 14 of the present specification), none of which is described by Blume.

Applicant acknowledges that Dansereau discloses a tablet comprising an outer tablet, comprising a first dose of an active ingredient, such as guaifenesin, in a pH independent hydrophilic polymer matrix, and an inner tablet, comprising a second dose of the active ingredient in a rapidly disintegrating excipient base and that Dansereau describes making the inner tablet composition by granulating guaifenesin with a portion of the polyvinylpyrrolidone, drying the granulation, and screening the dried granulation through a 12 mesh screen (see col. 6, lines 50-65 of Dansereau). Applicant submits that the disclosure of Dansereau broadly establishes only that 100% of the particles of Dansereau are less than 1680 microns in size (it is believed that the openings of a 12 mesh screen are 1680 microns in size) and Dansereau does not disclose or suggest that the screened guaifenesin /polyvinylpyrrolidone granulation satisfies the particle size distribution required by Applicant's claim 1. Applicant further submits that the process disclosed by Dansereau differs significantly from the process described in the present application and used to make the compositions of Applicant's Examples 1 -10. The process described by Dansereau differs from the process described in the present application with respect to, at least: (a) the wet milling of Applicant's agglomerate (see p. 9, lines 1 -11 of the present specification), (b) the selection of process conditions required to satisfy Applicant's claimed particle size distribution (see p. 10, line 12 to p. 11, line 8 of the present specification), and (c) the separation, dry milling, and subsequent reintroduction to Applicant's claimed composition of particles that initially exceeded a particle size classification limit

(see p. 3, lines 23- 25 and p. 10, lines 11 - 14 of the present specification), none of which is described by Dansereau.

Applicant submits that a person having ordinary skill in the art would not have found the present invention obvious in view of the disclosure of Blume and Dansereau because Blume fails to disclose the particle size distribution required by Applicant's claim 1 and Dansereau fails to remedy that deficiency, i.e., .Dansereau does not teach or, taken alone or in combination with Blume, suggest the particle size distribution required by Applicant's claim 1.

The Examiner further states that for the claimed additives such as glidants, lubricants, silica, stearic acid etc., Blume and Dansereau teach the conventional excipients including lubricants such as magnesium stearate, calcium stearate etc; binders such as povidone (polyvinylpyrrolidone), gelatin, starch; glidants such as talc or silicon dioxide, stabilizers and other excipients such as lactose, sorbitol etc. Accordingly, in the absence of evidence to the criticality of the specific excipients and their amounts (claims 3-4 & 33-34), it would have been obvious for one of an ordinary skill in the art at the time of the instant invention was made to the choose the appropriate excipient and optimize the amounts of the same in the composition of Blume with an expectation to achieve the desired effect.

The Examiner further urges that with respect to the claimed particle sizes, Blume teaches that no more than 30% granulation material passes through 100 mesh (150 microns) and not more than 10% retained on 10-mesh screen (greater than 850 microns) and that majority of the particles of Blume are thus in the range of 150 microns to 2 mm, with a smaller percentage of particles are below 150 microns. The Examiner points out that the maximum of 30% of the particles that pass through the 100-mesh screen, according to Blume, could be any size below 150 microns (as low as 45 microns claimed in the instant invention). The Examiner acknowledges that Blume does not teach the exact

percentages of particle sizes claimed in the instant application, but urges that in the absence of any unexpected results obtained with the claimed particle sizes and in particular, the percentages of particles, optimizing the sizes of the particles and the percentages of the particles of an agglomerated mixture of guaifenesin and methocel would have been obvious for one of an ordinary skill in the art at the time of the instant invention was made because Blume suggests a sustained release of the guaifenesin with the above process of preparation.

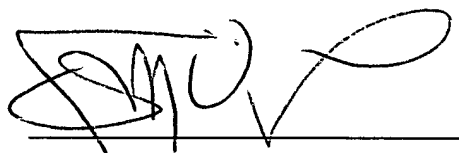
Applicant submits that it is believed that the openings in a 10 mesh screen are 2000 microns, rather than 850 microns, in size and further submits that the disclosure of Blume that "not more than about 30% of the resulting granulation comes through a 100 mesh screen and not more than about 10% of the resulting granulation is retained on 10-mesh screen" (see col. 8, lines 19-23 of Blume) establishes only that: (a) not more than about 10% particles of Blume are greater than 2000 microns in size, (b) not more than about 30% of particles of Blume are less than 150 microns in size, and thus (c) from about 60% to 100% of the particles of the composition of Blume are between 150 microns and 2000 microns in size.

Applicant further submits that, with respect to the additives and particle size distribution limitations of Applicant's claims, neither Blum nor Dansereau recognize the problems addressed by Applicant's invention, i.e., the sensitivity of guaifenesin compositions to processing conditions and difficulty in making satisfactory compressed guaifenesin dosage forms and the tendency of guaifenesin compositions to exhibit inadequate flow properties and to slow production of compressed guaifenesin dosage forms and of the need for guaifenesin compositions that offer both improved flow properties and improved robustness with regard to compression processing conditions (see p. 1, line 28 to p. 2 line 25 of the present application), and lacking any recognition of such problems, neither Blum nor Dansereau provides any motivation for seeking to further optimize composition or the particle size distribution of guaifenesin compositions of Blume or

Dansereau in a manner that would address such problems, and, even if it were obvious to try to further optimize the ingredients and/or particle size of the guaifenesin compositions of Blume or Dansereau, nothing in Blume or Dansereau would have led a person skilled in the art to the selection of ingredients or the particle size distribution claimed by Applicant.

For all the reasons discussed above, Applicant submits that the claims of the claims present application each patentably distinguish the present invention over the combined disclosure of Blume and Dansereau and therefore requests that the Examiner now reconsider and withdraw the rejection of claims 1-4, 6-9, and 31-36 of the present application under 35 U.S.C. 103(a) as being unpatentable over Blume in view of Dansereau and issue a notice of allowance for those claims.

Respectfully Submitted,

A handwritten signature in black ink, appearing to read 'K. McVeigh', written over a horizontal line.

Kevin E. McVeigh

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